What is claimed is:

1. A polypeptide comprising the amino acid sequence of a mammalian amyloid protein precursor (APP) or fragment thereof containing an APP cleavage site recognizable by a mammalian β-secretase, and further comprising two lysine residues at the carboxyl terminus of the amino acid sequence of the mammalian APP or APP fragment.

2. A polypeptide according to claim 1 comprising the amino acid sequence of a mammalian amyloid protein precursor (APP), and further comprising two lysine residues at the carboxyl terminus of the amino acid sequence of the mammalian amyloid protein precursor.

3. A polypeptide according to claim 1 wherein the polypeptide further includes a marker.

4. A polypeptide according to claim 3 wherein the marker comprises a reporter protein amino acid sequence attached to the APP amino acid sequence.

5. A polypeptide according to claim 4 wherein the reporter protein comprises an amino acid sequence of a fluorescing protein.

6. A polypeptide according to claim 1, wherein the mammalian APP is a human APP.

7. A polypeptide according to claim 6, wherein the human APP comprises at least one variation selected from the group consisting of a Swedish KM→NL mutation and a London V717→F mutation.

8. A polypeptide according to claim 6, wherein the human APP is selected from the group consisting of: an APP695 isoform, an APP 751 isoform, and an APP770 isoform.

9. A polypeptide according to claim 1 wherein the APP protein or fragment thereof comprises the APP-Sw β-secretase peptide sequence NLDA.

10. A polypeptide according to claim 9 wherein the APP protein or fragment thereof comprises the APP-Sw β-secretase peptide sequence SEVNLDAEFR (SEQ ID NO: 63).

11. A polypeptide according to claim 9 wherein the APP protein or fragment thereof further includes an APP transmembrane domain carboxy-terminal to the APP-Sw β-secretase peptide sequence.

12. A polypeptide according to claim 9 wherein the APP protein or fragment thereof comprises a chimeric APP, said chimeric APP including partial APP amino acid sequences from at least two species.

13. A polypeptide according to claim 12 wherein the chimeric APP includes amino acid sequence of a human APP and a rodent APP.

14. A polynucleotide comprising a nucleotide sequence that encodes a polypeptide according to any one of claims 1.

15. A vector comprising a polynucleotide according to claim 14.

16. A vector according to claim 15 wherein said polynucleotide is operably linked to a promoter to promote expression of the polypeptide encoded by the polynucleotide in a host cell.

17. A host cell transformed or transfected with a polynucleotide according to claim 14 or a vector according to claim 15 or 16.

18. A host cell according to claim 17 that is a mammalian cell.

19. A polypeptide useful for assaying for modulators of β-secretase activity, said polypeptide comprising an amino acid sequence of the formula NH_2-X-Y-Z-KK-COOH;

wherein X, Y, and Z each comprise an amino acid sequence of at least one amino acid;

wherein-NH_2-X comprises an amino-terminal amino acid sequence having at least one amino acid residue;

wherein Y comprises an amino acid sequence of a β-secretase recognition site of a mammalian amyloid protein precursor (APP); and

wherein Z-KK-COOH comprises a carboxy-terminal amino acid sequence ending in two lysine (K) residues.

20. A polypeptide according to claim 19 wherein the carboxyl-terminal amino acid sequence Z includes a hyrdrophobic domain that is a transmembrane domain in host cells that express the polypeptide.

21. A polypeptide according to claim 19 wherein the amino-terminal amino acid sequence X includes an amino acid sequence of a reporter protein.

22. A polypeptide according to claim 19 wherein the β-secretase recognition site Y comprises the human APP-Sw β-secretase peptide sequence NLDA.

23. A polynucleotide comprising a nucleotide sequence that encodes a polypeptide according to any one of claims 19-22.

24. A purified polypeptide comprising the murine Asp2 amino acid sequence set forth in SEQ ID NO: 8, or a fragment thereof that retains the β-secretase activity of said murine Asp2.

25. A polynucleotide comprising a nucleotide sequence that encodes the polypeptide of claim 24.

26. A polynucleotide according to claim 25 comprising the nucleotide sequence set forth in SEQ ID NO: 7.

27. A purified murine Asp2(b) polypeptide comprising the amino acid sequence set for in SEQ ID NO: 8 from residues 1-189 and 215-501, but lacking residues 190-214.

28. A polynucleotide comprising a nucleotide sequence that encodes the murine Asp2(b) polypeptide according to claim 27.

29. A vector comprising a polynucleotide according to claim 25.

30. A vector according to claim 29 wherein said polynucleotide is operably linked to a promoter to promote expression of the polypeptide encoded by the polynucleotide in a host cell.

31. A host cell transformed or transfected with a vector according to claim 30.

32. A host cell according to claim 31 that is a mammalian cell.

33. A host cell according to claim 31 that expresses the polypeptide on its surface.

34. A host cell according to claim 31, wherein the host cell is transfected with a nucleic acid comprising a nucleotide sequence that encodes an amyloid precursor protein (APP) that includes two carboxy-terminal lysine residues.

35. A host cell according to claim 34 that expresses the polypeptide and the APP on its surface.

36. A method of making a murine Asp2 polypeptide comprising steps of culturing a host cell of claim 61 in a culture medium under conditions in which the cell produces the polypeptide that is encoded by the polynucleotide.

37. A method according to claim 36, further comprising a step of purifying the polypeptide from the cell or the culture medium.

38. A host cell transformed or transfected with a polynucleotide according to claim 25.

39. A host cell according to claim 38 that is a mammalian cell.

40. A host cell according to claim 38 that expresses the polypeptide on its surface.

41. A host cell according to claim 38, wherein the host cell is transfected with a nucleic acid comprising a nucleotide sequence that encodes an amyloid precursor protein (APP) or fragment thereof containing a β-secretase cleavage site.

42. A host cell according to claim 41 wherein the APP includes two carboxy-terminal lysine residues.

43. A host cell according to claim 41 wherein the APP comprises the Swedish mutation (K→N, M→L) adjacent to the β-secretase cleavage site.

44. A host cell according to claim 41 that expresses the polypeptide and the APP on its surface.

45. A method of making a murine Asp2 polypeptide comprising steps of culturing a host cell of claim 38 in a culture medium under conditions in which the cell produces the polypeptide that is encoded by the polynucleotide.

46. A method according to claim 45, further comprising a step of purifying the polypeptide from the cell or the culture medium. –

47. A purified polypeptide comprising a fragment of a mammalian Asp2 protein, wherein said polypeptide lacks the Asp2 transmembrane domain of said Asp2 protein, and wherein the polypeptide and the fragment retain the β-secretase activity of said mammalian Asp2 protein.

48. A purified polypeptide according to claim 47 comprising a fragment of a human Asp2 protein that retains the β-secretase activity of said human Asp2 protein.

49. A purified polypeptide according to claim 48, wherein said polypeptide comprises a fragment of Asp2(a) having the amino acid sequence set forth in SEQ ID NO: 4, and wherein said polypeptide lacks transmembrane domain amino acids 455 to 477 of SEQ ID NO: 4.

50. A purified polypeptide according to claim 49, wherein said polypeptide further lacks cytoplasmic domain amino acids 478 to 501 of SEQ ID NO: 4.

51. A purified polypeptide according to claim 50, wherein said polypeptide further lacks amino acids 420-454 of SEQ ID NO: 4.

52. A purified polypeptide according to any one of claims 48-51, wherein said polypeptide comprises an amino acid sequence:

that includes amino acids 58 to 419 of SEQ ID NO: 4, and

that lacks amino acids 22 to 57 of SEQ ID NO: 4.

53. A purified polypeptide according to any one of claims 48-51, wherein said polypeptide comprises an amino acid sequence:

that includes amino acids 46 to 419 of SEQ ID NO: 4, and

that lacks amino acids 22 to 45 of SEQ ID NO: 4.

54. A purified polypeptide according to claim 49, wherein said polypeptide comprises an amino acid sequence that includes amino acids 22 to 454 of SEQ ID NO: 4.

55. A purified polypeptide according to claim 47 comprising the amino acid sequence of human Asp-2(b) protein set forth as SEQ ID NO: 6, or fragments thereof that retain β-secretase activity.

56. A purified polypeptide according to claim 48, wherein said polypeptide comprises a fragment of Asp2(b) having the amino acid sequence set forth in SEQ ID NO: 6, and wherein said polypeptide lacks transmembrane domain amino acids 430 to 452 of SEQ ID NO: 6.

57. A purified polypeptide according to claim 56, wherein said polypeptide further lacks cytoplasmic domain amino acids 453 to 476 of SEQ ID NO: 6.

58. A purified polypeptide according to claim 57, wherein said polypeptide further lacks amino acids 395-429 of SEQ ID NO: 4.

59. A purified polypeptide according to any one of claims 56-58, wherein said polypeptide comprises an amino acid sequence:

that includes amino acids 58 to 394 of SEQ ID NO: 4, and

that lacks amino acids 22 to 57 of SEQ ID NO: 4.

60. A purified polypeptide according to any one of claims 56-58, wherein said polypeptide comprises an amino acid sequence:

that includes amino acids 46 to 394 of SEQ ID NO: 4, and

that lacks amino acids 22 to 45 of SEQ ID NO: 4.

61. A purified polypeptide according to claim 56, wherein said polypeptide comprises an amino acid sequence that includes amino acids 22 to 429 of SEQ ID NO: 6.

62. A polypeptide comprising an amino acid sequence at least 95% identical to a fragment of a human Asp2 protein, wherein said polypeptide and said fragment lack a transmembrane domain and retain β-secretase activity of the human Asp2 protein.

63. A purified polynucleotide comprising a nucleotide sequence that encodes the polypeptide of any one of claims 47-63.

64. A polynulcleotide of claim 47 wherein the polypeptide comprises a fragment of human Asp2 protein.

65. A polynucleotide of claim 64 wherein the polypeptide comprises a fragment of Asp2(a) having the amino acid sequence set forth as SEQ ID NO: 4, and

wherein the polypeptide lacks the transmembrane domain amino acids 455-477 of SEQ ID NO: 4.

66. A polynucleotide of claim 64, wherein the polypeptide further lacks cytoplasmic domain amino acids 478-501 of SEQ ID NO: 4.

67. A purified polynucleotide of claim 66, wherein said polypeptide further lacks amino acids 420-454 of SEQ ID NO: 4.

68. A polynucleotide of claim 65, wherein the polypeptide comprises an amino acid sequence:

that includes amino acids 58-419 of SEQ ID NO: 4, and

that lacks amino acids 22-57 of SEQ ID NO: 4.

69. A polynucleotide of claim 65, wherein the polypeptide comprises an amino acid sequence:

that includes amino acids 46-419 of SEQ ID NO: 4, and

that lacks amino acids 22-45 of SEQ ID NO: 4.

70. A polynucleotide of claim 65, wherein the polypeptide comprises an amino acid sequence that includes amino acids 22-454 of SEQ ID NO: 4.

71. A polynucleotide of claim 64, wherein the polypeptide comprises a fragment of human Asp2(b) having the amino acid set forth in SEQ ID NO: 6, and wherein the polypeptide lacks transmembrane domain amino acids 430-452 of SEQ ID NO: 6.

72. A polynucleotide of claim 71, wherein the polypeptide lacks cytoplasmic domain amino acids 453-476 of SEQ ID NO: 6.

73. A polynucleotide of claim 72, wherein the polypeptide further lacks amino acids 395-429 of SEQ ID NO: 6.

74. A polynucleotide of claim 71, wherein the polypeptide comprises an amino acid sequence:

that includes amino acids 58-394 of SEQ ID NO: 6, and

that lacks amino acids 22 to 57 of SEQ ID NO: 6.

75. A polynucleotide of claim 71, wherein the polypeptide comprises an amino acid sequence:

that includes amino acids 46-394 of SEQ ID NO: 6, and

that lacks amino acids 22-45 of SEQ ID NO: 6.

76. A polynucleotide of claim 71, wherein the polypeptide comprises an amino acid sequence that includes amino acids 22 to 429 of SEQ ID NO: 6.

77. A vector comprising a polynucleotide according to claim 63.

78. A host cell transformed or transfected with a polynucleotide according to claim 63.

79. A host cell transformed or transfected with a vector of claim 77.

80. A polynucleotide comprising a nucleotide sequence that hybridizes under stringent conditions to a nucleic acid comprising the sequence set forth in SEQ ID NO: 4 or SEQ ID NO: 6, wherein the nucleotide sequence encodes a polypeptide having β-secretase biological activity.

81. A vector comprising a polynucleotide of claim 80.

82. A host cell transformed or transfected with a polynucleotide of claim 80.

83. A method for assaying for modulators of β-secretase activity, comprising the steps of:

(a) contacting a first composition with a second composition both in the presence and in the absence of a putative modulator compound, wherein the first composition comprises a mammalian β-secretase polypeptide or biologically active fragment thereof, and wherein the second composition comprises a substrate polypeptide having an amino acid sequence comprising a β-secretase cleavage site;

(b) measuring cleavage of the substrate polypeptide in the presence and in the absence of the putative modulator compound; and

(c) identifying modulators of β-secretase activity from a difference in cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a β-secretase antagonist reduces such cleavage and a modulator that is a β-secretase agonist increases such cleavage.

84. A method according to claim 83, wherein the first composition comprises a purified human Asp2 polypeptide.

85. A method according to claim 83, wherein the first composition comprises a soluble fragment of a human Asp2 polypeptide that retains Asp2 β-secretase activity.

86. A method according to claim 85 wherein the soluble fragment is a fragment lacking an Asp2 transmembrane domain.

sub A27

87. A method according to claim 83, wherein the substrate polypeptide of the second composition comprises the amino acid sequence SEVNLDAEFR.

Sub A2 Cont.

88. A method according to claim 83, wherein the substrate polypeptide of the second composition comprises the amino acid sequence EVKMDAEF.

89. A method according to claim 83, wherein the second composition comprises a polypeptide having an amino acid sequence of a human amyloid precursor protein (APP).

90. A method according to claim 89, wherein the human amyloid precursor protein is selected from the group consisting of: APP695, APP751, and APP770.

91. A method according to claim 90, wherein the human amyloid precursor protein includes at least on mutation selected from a KM→NL Swiss mutation and a V→F London mutation.

92. A method according to claim 89, wherein the polypeptide having an amino acid sequence of a human APP further comprises an amino acid sequence comprising a marker sequence attached amino-terminal to the amino acid sequence of the human amyloid precursor protein.

93. A method according to claim 89, wherein the polypeptide having an amino acid sequence of a human APP further comprises two lysine residues attached to the carboxyl terminus of the amino acid sequence of the human APP.

94. A method according to claim 82, wherein the second composition comprises a eukaryotic cell that expresses amyloid precursor protein (APP) or a fragment thereof containing a β-secretase cleavage site.

95. A method according to claim 94, wherein the APP expressed by the host cell is an APP variant that includes two carboxyl-terminal lysine residues.

96. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) contacting amyloid precursor protein (APP) and purified and isolated Hu-Asp2 in the presence and absence of a test agent;

(b) determining the APP processing activity of the Hu-Asp2 in the presence and absence of the test agent; and

(c) comparing the APP processing activity of the Hu-Asp2 polypeptide in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits the APP processing activity of Hu-Asp2, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

97. A method according to claim 96, wherein the Hu-Asp2 comprises a polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the Hu-Asp2.

98. A method according to claim 60 wherein the nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to the complement of a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

99. A method according to claim 97 wherein the Hu-Asp2 comprises the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4.

100. A method according to claim 97, wherein the Hu-Asp2 comprises the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6.

101. A method according to claim 97, wherein the Hu-Asp2 comprises a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b).

102. A method according to claim 96, wherein the APP comprises the Swedish mutation (K→N, M→L) adjacent to the β-secretase processing site.

103. A method according to claim 96, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

104. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) contacting Hu-Asp2 and amyloid precursor protein (APP) in the presence and absence of a test agent, wherein the APP comprises a carboxy-terminal di-lysine (KK) and wherein the contacting comprises growing a host cell that expresses the APP in the presence and absence of the test agent;

(b) determining the APP processing activity of the Hu-Asp2 in the presence and absence of the test agent; and

(c) comparing the APP processing activity of the Hu-Asp2 polypeptide in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced

activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

105. A method according to claim 104, wherein the APP further comprises the Swedish mutation (K→N, M→L) adjacent to the β-secretase processing site.

106. A method according to claim 104, wherein the host cell has been transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes a Hu-Asp2, wherein said nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to the complement of a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

107. A method according to claim 104, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

108. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) contacting Hu-Asp2 and amyloid precursor protein (APP) in the presence and absence of a test agent, wherein the contacting comprises

growing a host cell transformed or transfected with a polynucleotide comprising a nucleotide sequence encoding the Hu-Asp2 in the presence and absence of the test agent;

(b) determining the APP processing activity of the Hu-Asp2 in the presence and absence of the test agent; and

(c) comparing the APP processing activity of the Hu-Asp2 polypeptide in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

109. A method according to claim 108, wherein the host cell expresses APP.

110. A method according to claim 109 wherein the determining step comprises measuring the production of amyloid beta peptide by the cell in the presence and absence of the test agent.

111. A method according to claim 109, wherein the host cell expresses an APP having an amino acid sequence that includes a carboxy-terminal di-lysine.

112. A method according to claim 109, wherein the host cell expresses an APP comprising the Swedish mutation (K→N, M→L) adjacent to the β-secretase processing site.

113. A method according to claim 108, wherein the host cell is a human embryonic kidney cell line 293 (HEK293) cell.

114. A method according to claim 108 wherein the nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to the complement of a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

115. A method according to claim 108, wherein the host cell comprises a vector that comprises the polynucleotide.

116. A method according to claim 108 wherein the polynucleotide comprises a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4.

117. A method according to claim 108 wherein the polynucleotide comprises a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6.

118. A method according to claim 108 wherein the polynucleotide comprises a nucleotide sequence encoding a polypeptide comprising a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b).

119. A method according to claim 108 wherein the Hu-Asp2 is encoded by a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to the complement of a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

120. A method according to claim 108, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

121. A method for identifying agents that modulate the activity of Asp2 aspartyl protease, comprising the steps of:

(a) contacting an Asp2 aspartyl protease and amyloid precursor protein (APP) in the presence and absence of a test agent, wherein the Asp2 aspartyl protease is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to the complement of a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5;

(b) determining the APP processing activity of the Asp2 aspartyl protease in the presence and absence of the test agent; and

(c) comparing the APP processing activity of the Asp2 aspartyl protease in the presence of the test agent to the activity in the absence of the agent to identify agents that modulate the activity of the Asp2 aspartyl protease, wherein a modulator that is an Asp2 inhibitor reduces APP processing and a modulator that is an Asp2 agonist increases such processing.

122. A method according to claim 121, wherein the Asp2 aspartyl protease is purified and isolated.

123. A method according to claim121, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

124. A method for identifying an agent that inhibits APP processing activity of human Asp2 aspartyl protease, comprising steps of:

(a) contacting Hu-Asp2 with an APP substrate for the Hu-Asp2, in the presence and absence of a test agent;

(b) determining the proteolytic processing of the APP substrate by the Hu-Asp2 in the presence and absence of the test agent; and

(c) comparing the proteolytic processing of the APP substrate by the Hu-Asp2 in the presence and absence of the test agent to identify an agent that inhibits the APP processing activity of Hu-Asp2, wherein reduced proteolytic processing of the APP substrate by the Hu-Asp2 in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

125. A method according to claim 124, wherein the APP substrate is a peptide comprising a β-secretase cleavage site of APP.

126. A method according to claim 125, wherein the β-secretase cleavage site comprises the formula P2-P1-P1'-P2', wherein

P2 is an amino acid selected from K and N;

P1 is an amino acid selected from M and L;

P1' is the amino acid D; and

P2' is the amino acid A.

127. A method according to claim 125, wherein the peptide comprises the amino acid sequence KMDA (SEQ ID NO: 64, positions 4-7).

128. A method according to claim 126, wherein the peptide comprises the amino acid sequence EVKMDAEF (SEQ ID NO: 67).

129. A method according to claim 125, wherein the peptide comprises the amino acid sequence NLDA (SEQ ID NO: 66).

130. A method of reducing cellular production of amyloid beta (Aβ) from amyloid precursor protein (APP), comprising step of transforming or transfecting cells with an anti-sense reagent capable of reducing Asp2 polypeptide production by reducing Asp2 transcription or translation in the cells, wherein reduced Asp2 polypeptide production in the cells correlates with reduced cellular processing of APP into Aβ.

131. A method according to claim 130, wherein the cell is a neural cell.

132. A method according to claim 130, wherein the anti-sense reagent comprises an oligonucleotide comprising a single stranded nucleic acid sequence capable of binding to a Hu-Asp mRNA.

133. A method according to claim 130, wherein the anti-sense reagent comprises an oligonucleotide comprising a single stranded nucleic acid sequence capable of binding to a Hu-Asp DNA.

134. A method of reducing cellular production of amyloid beta (Aβ) from amyloid precursor protein (APP), comprising steps of:

(a) identifying mammalian cells that produce Aβ; and

(b) transforming or transfecting the cells with an anti-sense reagent capable of reducing Asp2 polypeptide production by reducing Asp2 transcription or translation in the cells, wherein reduced Asp2 polypeptide production in the cells correlates with reduced cellular processing of APP into Aβ.

135. A method according to claim 134, wherein the cell is a neural cell.

136. A method according to claim 134, wherein the anti-sense reagent comprises an oligonucleotide comprising a single stranded nucleic acid sequence capable of binding to a Hu-Asp mRNA.

137. A method according to claim 133, wherein the anti-sense reagent comprises an oligonucleotide comprising a single stranded nucleic acid sequence capable of binding to a Hu-Asp DNA.

138. A method according to claim 133, wherein the identifying step comprises diagnosing Alzheimer's disease, where Alzheimer's disease correlates with the existence of cells that produce Aβ that forms amyloid plaques in the brain.

139. A vector comprising a polynucleotide according to claim 22.

140. A host cell comprising a vector according to claim 139.

141. A purified polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 8.

142. A polypeptide comprising an amino acid sequence at least 95% identical to a polypeptide according to any one of claims 42-61, wherein said polypeptide lacks a transmembrane domain and retains β-secretase activity of a human Asp2 protein.

143. A method according to claim 83, wherein the first composition comprises a human Asp2 polypeptide of any one of claims 1-13, 19-24, 26-27 or 47-62.

144. A method according to claim 124 wherein the Hu-Asp2 is purified and isolated.

145. A method according to claim 124, wherein the Hu-Asp2 is encoded by a nucleic acid that hybridizes under stringent hybridization conditions to the complement of a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

146. A method according to claim 124, wherein the Hu-Asp2 is selected from the group consisting of:

(a) Hu-Asp2(a) comprising the amino acid sequence set forth in SEQ ID NO: 4;

(b) Hu-Asp2(b) comprising the amino acid sequence set forth in SEQ ID NO: 6; and

(c) fragments of Hu-Asp2(a) (SEQ ID NO: 4) and Hu-Asp2(b) (SEQ ID NO: 6) that cleave the APP substrate at a β-secretase cleavage site.

147. A method according to claim 87, wherein the Hu-Asp2 comprises an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 4 and 6.

148. A method according to claim 146, wherein the Hu-Asp2 comprises a soluble fragment of Hu-Asp2(a) or Hu-Asp2(b) that lacks an Asp2 transmembrane domain.

149. A method according to claim 148, wherein the Hu-Asp2 has an amino acid sequence consisting of a sequence-selected from the group consisting of SEQ ID NOS: 30, 32, 51, and 53.

150. A method according to claim 148, wherein the Hu-Asp2 comprises a fragment of Hu-Asp2(a) or Hu-Asp2(b), wherein the Hu-Asp 2 lacks amino acids 1-45 of SEQ ID NOS: ~~4 or~~ 6.

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